Second tumor induction after RT

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Indice della lezione

1. **Il meccanismo del danno**
2. **I dati clinici**
3. **Il dibattito**
   - IMRT vs 3DCRT
   - Hypo vs. Normo fractionation

1.Il meccanismo del danno

Il meccanismo del danno

L'induzione di un secondo tumore appartiene alla categoria del danno stocastico da radiazioni.

Questa categoria di danno riguarda tipicamente dosi da 0,05 Sv a qualche Sv, mentre le dosi da Radioterapia sono di almeno 1/ 2 ordini di grandezza superiori (anche se frazionate e se su volumi dell'ordine della decina o centinaia di cc).

La limitazione del volume irradiato porta a valori della dose dei principali OAR tipici dell'ambito del danno stocastico, anche se all'interno del volume compreso dalle isodosi alte si verifica la copresenza di effetti tipici del danno deterministico

Danno stocastico

Nell'ambito quindi di questa lezione vorremmo occuparci della valutazione del danno stocastico

Ovvero di dose integrali fino a 1 – 2 Sv

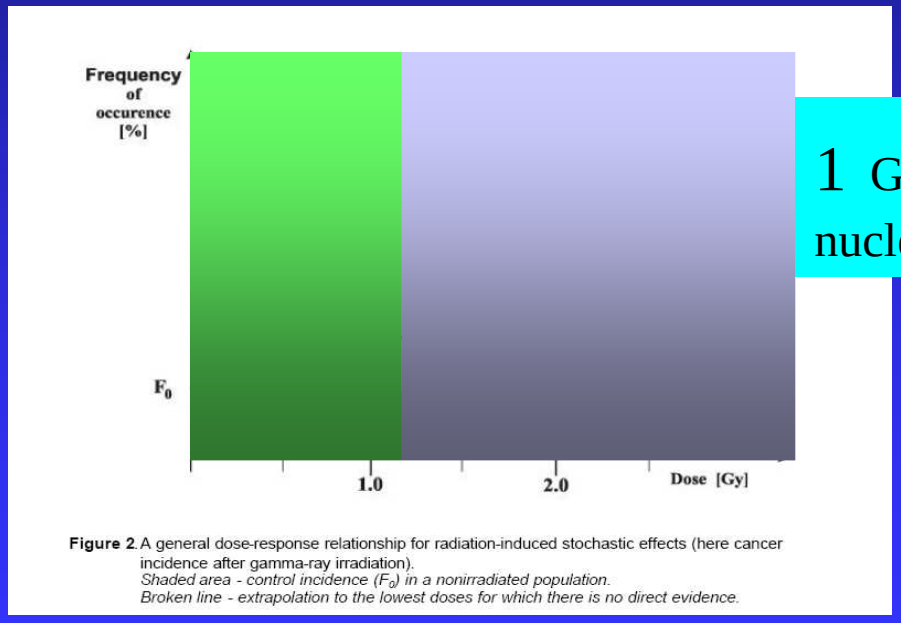


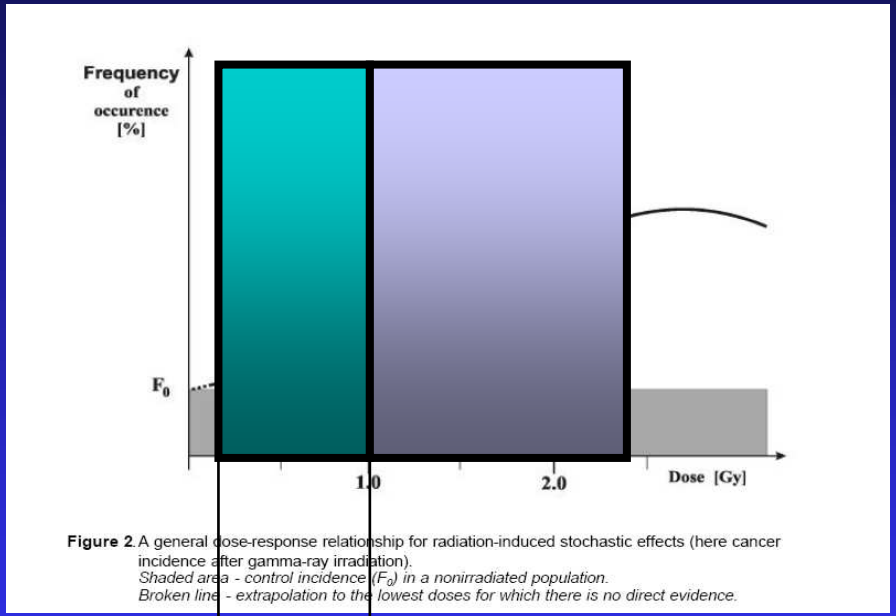
Figure 2. A general dose-response relationship for radiation-induced stochastic effects (here cancer incidence after gamma-ray irradiation).
Shaded area - control incidence (F_0) in a nonirradiated population.
Broken line - extrapolation to the lowest doses for which there is no direct evidence.

1 Gy = 10^4 ionizzazioni nel nucleo cellulare

Il modello di correlazione

Andamento Quadratico ?

Relazione dose-effetto lineare (passante per l'origine; validità provata tra 0,1 e 2 Sv)



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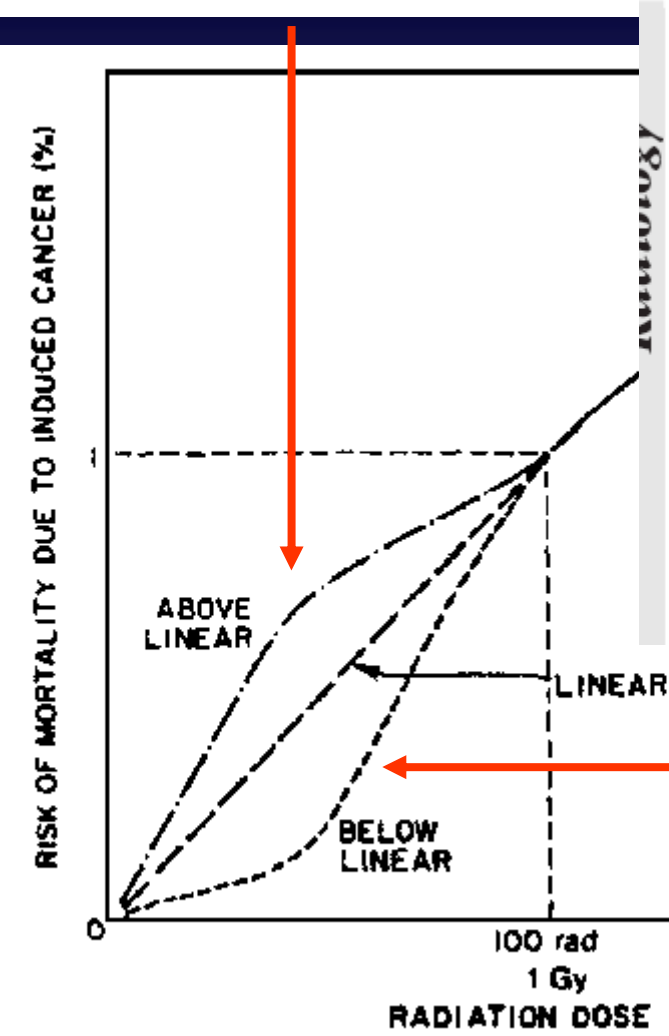
Linearità dimostrata

solo per dosi superiori a 0.2 Sv è stata dimostrata una correlazione statisticamente significativa per (l'aumento) dell'incidenza di neoplasie .
(M. Tubiana , IJROBP, 2005)

Andamento sovralineare



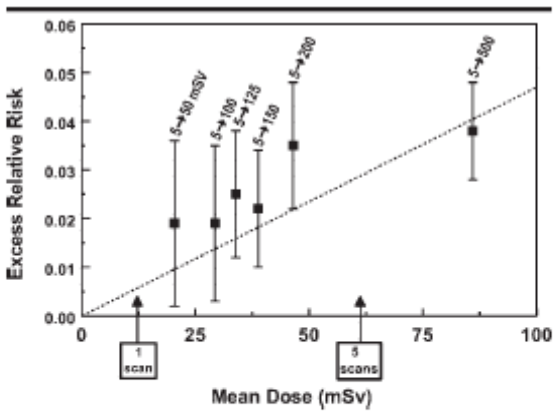
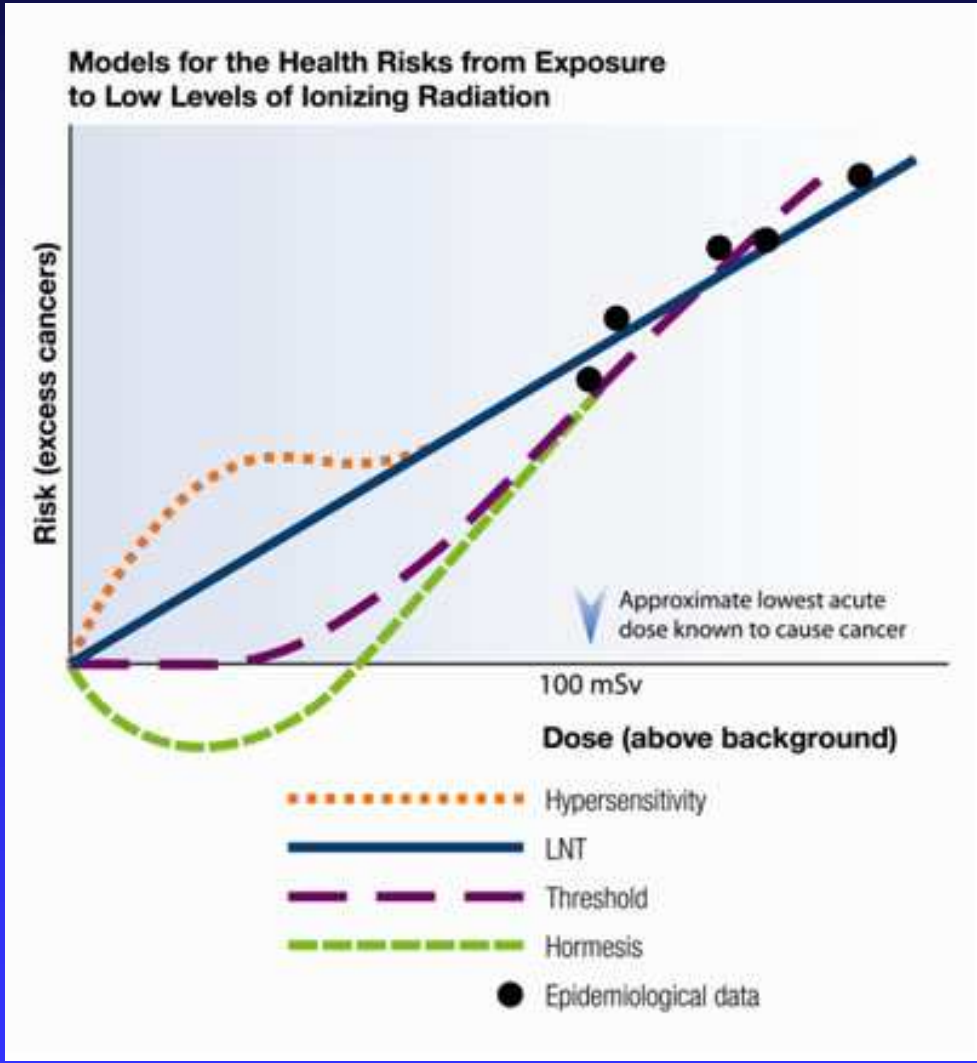


Figure 1. Graph shows estimated excess relative risk (■) (±1 standard error [error bars]) of mortality (1950–1997) from solid cancer among groups of survivors in the life-span study cohort of atomic bomb survivors who were exposed to low doses (<500 mSv) of radiation (10). Dose limits for each group are shown above each data point. Dashed line represents result of zero-intercept linear fit (10) to all life-span study data from 5 to 4,000 mSv (higher dose points not shown). Arrows refer to estimated effective doses from one and five full-body CT examinations.

Andamento sottolinear

O addirittura !!



L'inferenza da alte a basse dosi (da 1 Gy a 10 mGy)

Apparentemente il modello potrebbe giustificare una sua estensione fino a 0,1 Gy , ma sembrerebbe arbitraria la sua estensione a dosi

0,01 – 0,001 Gy

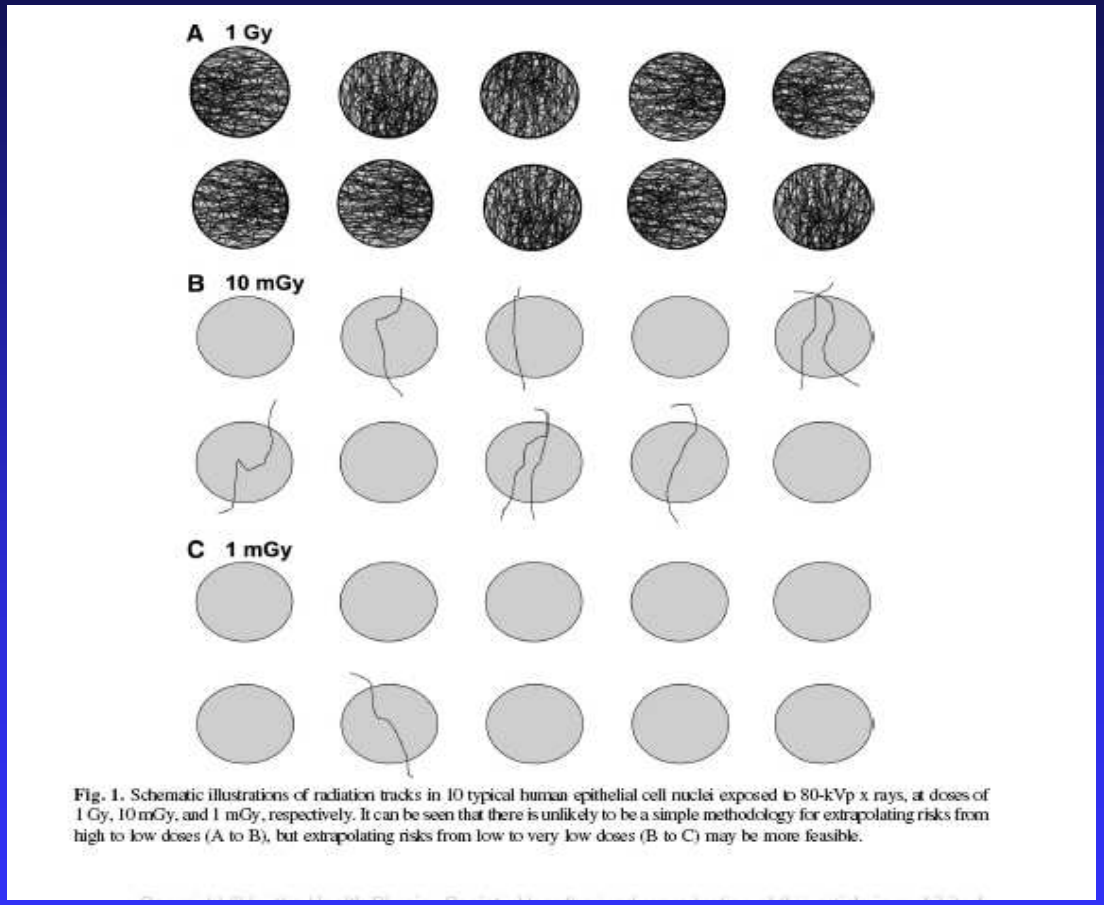


Fig. 1. Schematic illustrations of radiation tracks in 10 typical human epithelial cell nuclei exposed to 80-kVp x rays, at doses of 1 Gy, 10 mGy, and 1 mGy, respectively. It can be seen that there is unlikely to be a simple methodology for extrapolating risks from high to low doses (A to B), but extrapolating risks from low to very low doses (B to C) may be more feasible.

D.J.Brenner; Health Physics, 2009

1 Gy = 10^4 ionizzazioni per nucleo
40 double strand breaks
1000 tracks per nucleus

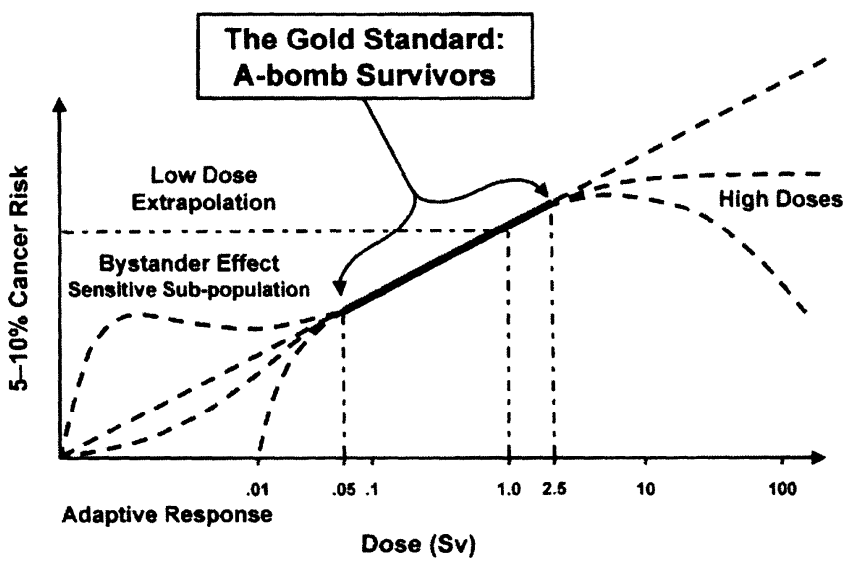
La non linearità della realtà

Il meccanismo del danno cambia da un modello a molti colpi ad un modello a pochi colpi (per nucleo),passando da 0,1 Gy a 0,01 Gy ed oltre

La linearità inoltre non considererebbe:

- **Bystander effect** (sicuramente influenza non lineare ma non si sa se in sovra o sottolinearità alle basse dosi < 0,01Gy)
- **Immune surveillance** : sicuramente sovralineare alle basse dosi
- **Different Biological responses** : individua una sicura non linearità nel tratto tra 10 mGy e 1mGy dovuta ad una variazione dei meccanismi del danno

Classical models



Are no longer acceptable risk evaluations when based on target mean dose or integral dose

Schneider ESTRO 2007

$$D_{eff} = \sum_i D_i w_i$$

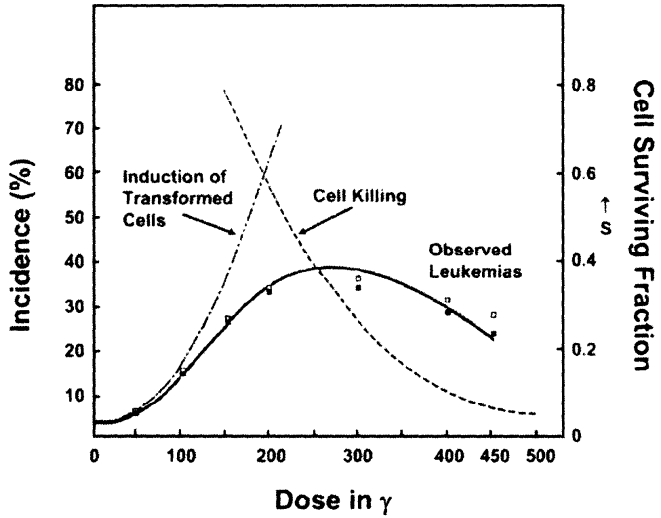
$$P = KD_{eff}$$

Table 3. Recommended tissue weighting factors.

Tissue	w_T	$\sum w_T$
Bone-marrow (red), Colon, Lung, Stomach, Breast, Remainder Tissues*	0.12	0.72
Gonads	0.08	0.08
Bladder, Oesophagus, Liver, Thyroid	0.04	0.16
Bone surface, Brain, Salivary glands, Skin	0.01	0.04

*Remainder Tissues: Adrenals, Extrathoracic (ET) region, Gall bladder, Heart, Kidneys, Lymphatic nodes, Muscle, Oral mucosa, Pancreas, Prostate (♂), Small intestine, Spleen, Thymus, Uterus/cervix (♀).

Leukemia from Whole Body Irradiation of Mice (Gray, 1957)



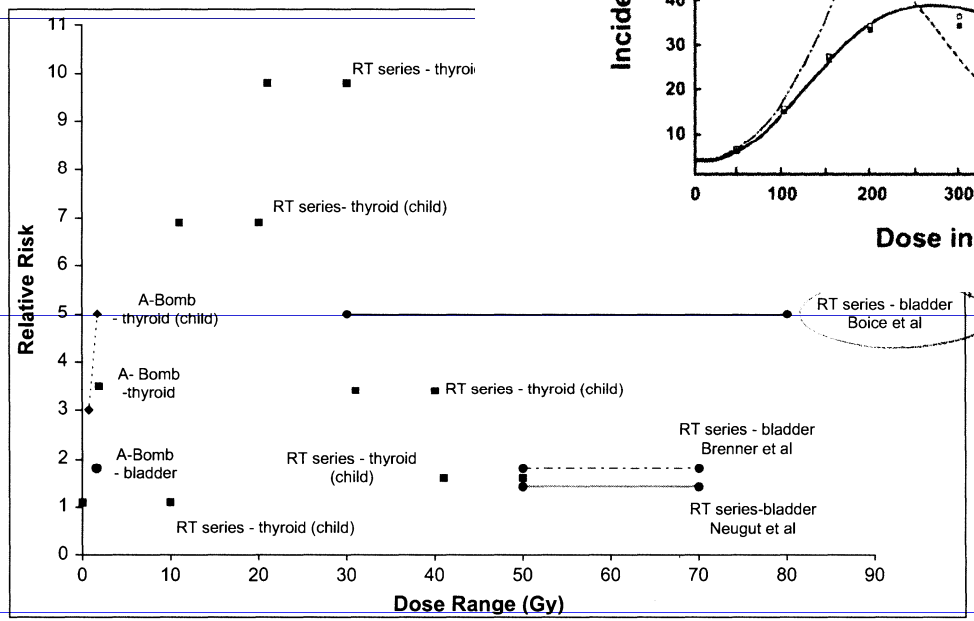
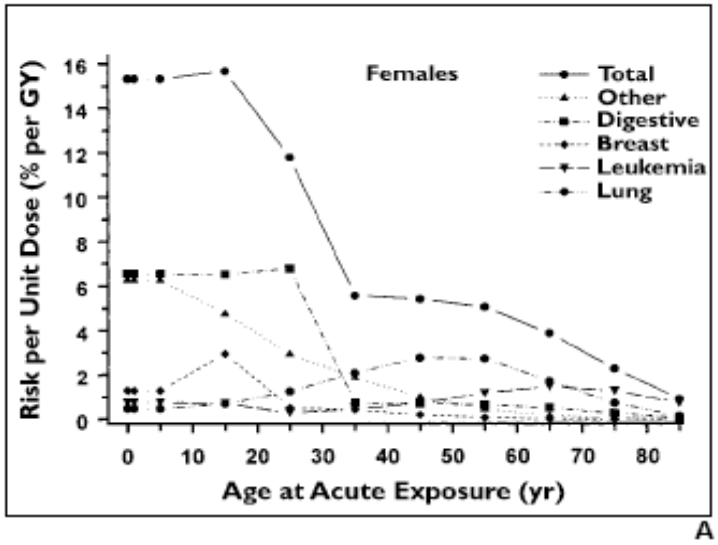


Fig. 2. Clinical studies using adequate patient numbers, follow-up periods, and control groups show an increased risk of cancer induction by radiotherapy. Studies by Brenner *et al.* (20), Boice *et al.* (21), and Neugut *et al.* (19) suggest a risk in therapy patients similar to that for A-bomb survivors (38, 39) who received low doses only. They therefore support a plateauing of risk above 2 to 3-Gy single fraction whole-body exposure. Data from Boice *et al.* (21) regarding leukemic risk and from Sigurdson *et al.* (25) regarding thyroid cancer induction in children exposed to radiotherapy suggest a reduction in carcinogenesis at higher doses

Andamenti del rischio per organi ed età diverse



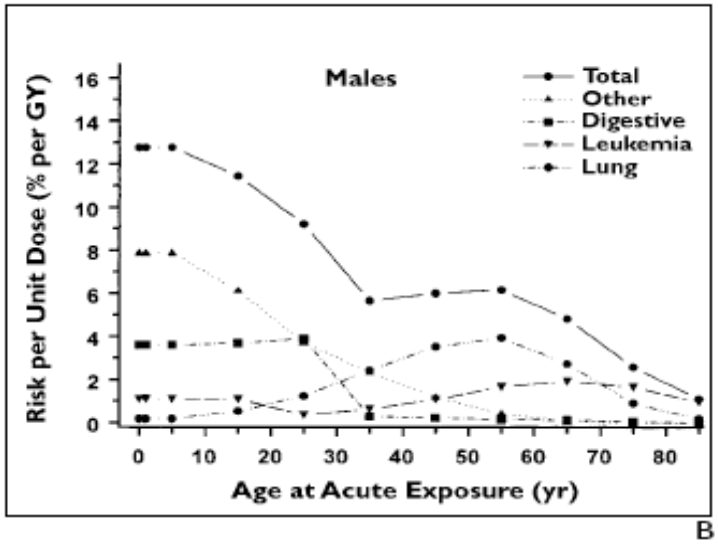


Fig. 4.—Breakdown by cancer type.
A and B, Graphs show breakdown by cancer type of risk per unit dose for females (A) and males (B) of lifetime attributable cancer mortality risks as a function of age at a single acute exposure as estimated by the National Academy of Sciences BEIR V (Biological Effects of Ionizing Radiations) committee [12].

David j. Brenner et al; Estimated Radiation Risks potentially associated with Full Body CT Screening; Radiology 232(2004); 735 -738

OED

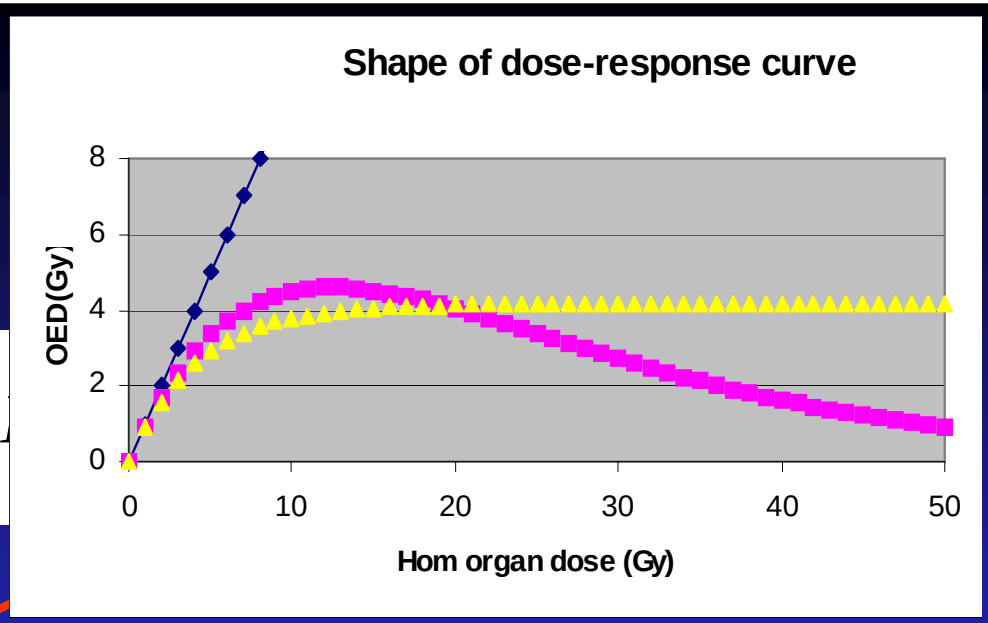
OED definition:

Two different 3D dose distributions have the same OED if they cause the same radiation induced cancer incidence

Schneider U. et al, IJROBP, 2005(51), 1510 -1515

OED FORMALISM

$$OED = \frac{1}{V}\sum_i DVH($$



$$P(D_i) = KD$$

$$P(D_i) = e^{-\alpha D_i}$$

$$P(D_i) = \frac{(1-e^{-\delta D_i})}{D_i}$$

Hp linear

Hp bell shaped

plateu

Schneider U. et al, IJROBP, 2005(51), 1510 -1515

OED Results in Prostate RT

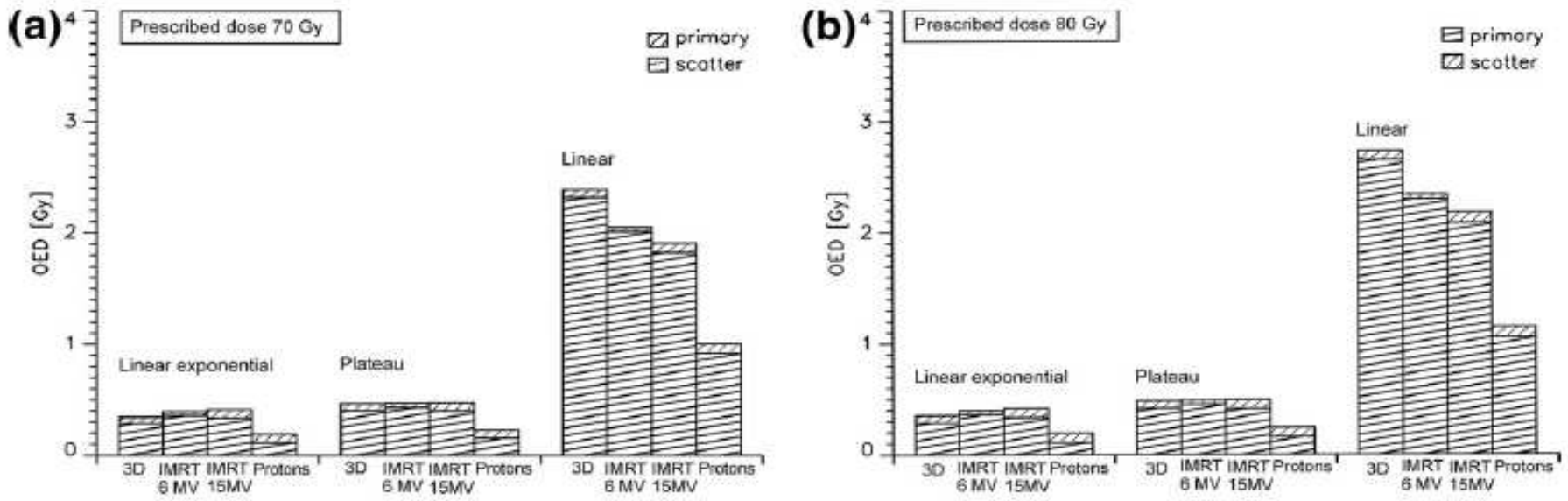


Fig. 2. Organ equivalent dose (OED) for different treatment techniques and dose–response relationships applied to prostate radiotherapy, for (a) 70-Gy and (b) 80-Gy target dose. The part of the bar indicated by solid lines shows the OED that corresponds to the primary dose distribution, and the bars with the dotted lines to X-ray scatter and neutrons. IMRT = intensity-modulated radiotherapy.

Schneider U. et al; The impact of dose escalation in secondary cancer risk after prostate RT; IJROBP 68(3); 2007

Our results

Head & Neck

Linac IMRT

OED lin (Gy)	OED bell (Gy)	OED plateau (Gy)
2,21	0,27	0,38

TOMO HT

OED lin (Gy)	OED bell (Gy)	OED plateau (Gy)
2,36	0,31	0,42

Prostate

Linac 3DCRT

OED lin (Gy)	OED bell (Gy)	OED plateau (Gy)
1,76	0,23	0,32

TOMO HT

OED lin (Gy)	OED bell (Gy)	OED plateau (Gy)
1,97	0,36	0,43

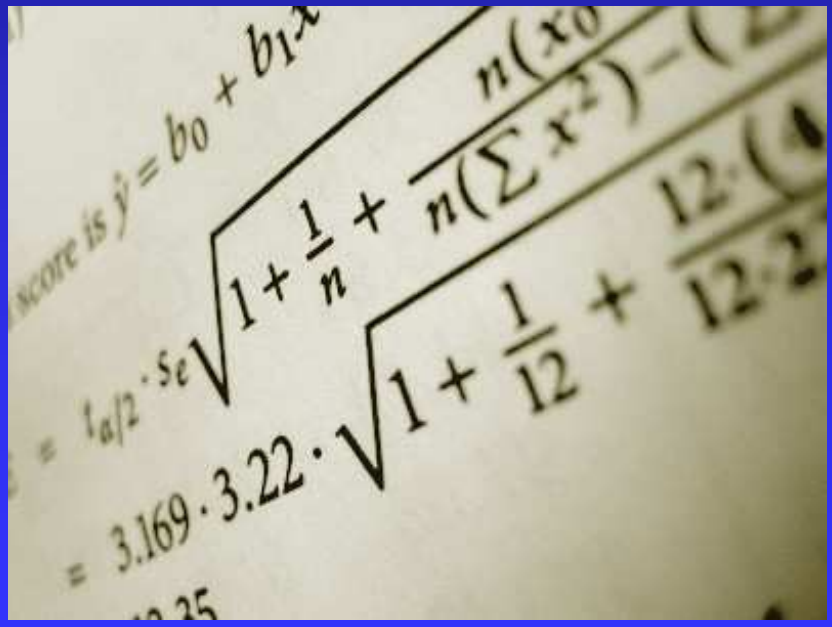
Limits of OED Modelling

Does not consider the different radiosensitivity of different organs

Does not consider different class of age for different radiosensitivity

Does not consider different tumors

2. CLINICAL Data



A common Language

Relative Risk : Is the risk of an event relative to the exposure. Is the ratio of the probability of the event occurring in the exposed group versus non exposed group.

$$RR = \frac{Inc_{RT}}{Inc_{surg}}$$

The relative risk is a comparison between different risk levels. For example, your relative risk for lung cancer is (approximately) 10 if you have every smoked, compared to a nonsmoker. This means you are 10 times as likely to get lung cancer. If the risk is about one percent for a nonsmoker, this translates to about 10 percent for a person who has smoked (it is even higher for heavy smokers).

A common Language

Absolute risk : is risk stated without any context.

A 10 percent increase (relative risk of 1.1) in brain tumors means .10 x 6 = .6 new cases per 100,000 people. On the other hand, a 10 percent increase in breast cancer affects 134 per 100,000 people.

Therefore the right figure of the enhancement of the risk is defined as :

$$[(RR-1)*AR]$$

A common Language

ODDs Ratio (OR)

$$\frac{\frac{p}{(1-p)}}{\frac{p'}{(1-p')}}$$

E' un rapporto tra odds ; ovvero tra probabilità di un evento ed il suo complementare. Nel nostro caso riguarderà I rapporti degli ODDS tra esposti a radiazioni ed una categoria medesima dal punto di vista diagnostico , ma non esposta . Tipicamente RT vs Chir.

Prostate data from literature

TABLE 2
Comparison of Risks of Developing Second Malignancies for Prostate Carcinoma Patients Treated with Radiotherapy versus Surgery Only, As a Function of Time after Diagnosis

	Radiotherapy			Surgery			Radiotherapy vs. surgery		
Second malignancy[a]	Observed	Expected	$(O/E)_{RT}$	Observed	Expected	$(O/E)_{surgery}$	% increase in risk: RT vs. surgery[b]	95% CI of % increase in risk	*P* value
All second malignancies[c] (all yrs)	3549	3991	0.89	5055	5914	0.86	4	[−1, 9]	0.08
≥ 5 yrs	1185	1285	0.92	1646	2008	0.82	11	[3, 20]	0.007
≥ 10 yrs	305	318	0.96	393	528	0.75	27	[9, 48]	0.002
All solid tumors[d] (all yrs)	3171	3589	0.88	4441	5305	0.84	6	[1, 11]	0.02
≥ 5 yrs	1065	1152	0.92	1432	1797	0.80	15	[6, 24]	0.0009
≥ 10 yrs	280	284	0.99	344	471	0.73	34	[14, 57]	0.0004
Bladder (all yrs)	455	414	1.10	608	628	0.97	15	[2, 31]	0.02
≥ 5 yrs	164	137	1.20	168	219	0.77	55	[24, 92]	0.0001
≥ 10 yrs	46	35	1.32	44	59	0.75	77	[14, 163]	0.01
Rectum (all yrs)	198	242	0.82	298	363	0.82	−2	[−18, 18]	0.87
≥ 5 yrs	73	77	0.95	86	121	0.71	35	[−1, 86]	0.06
> 10 yrs	22	19	1.18	17	31	0.55	105	[9, 292]	0.03
Colon (all yrs)	541	584	0.93	823	903	0.91	0	[−10, 12]	0.97
≥ 5 yrs	178	196	0.91	266	317	0.84	7	[−11, 30]	0.47
> 10 yrs	45	50	0.91	63	85	0.74	24	[−16, 81]	0.29
Lung (all yrs)	845	1050	0.80	1087	1485	0.73	11	[1, 21]	0.03
≥ 5 yrs	302	328	0.92	369	491	0.75	22	[5, 42]	0.01
≥ 10 yrs	79	79	1.01	88	126	0.70	42	[5, 93]	0.02
Sarcomas in field (all yrs)	38	21	1.80	32	31.4	1.02	85	[15, 201]	0.01
≥ 5 yrs	17	6.8	2.50	11	10.7	1.03	145	[15, 444]	0.02
≥ 10 yrs	5	1.7	2.91	3	2.9	1.05	217	[−23, 1461]	0.11
Distant sarcomas (all yrs)	31	22	1.40	32	33.2	0.97	51	[−9, 152]	0.11
≥ 5 yrs	10	7.2	1.39	11	11.5	0.96	36	[−44, 225]	0.49
≥ 10 yrs	2	1.9	1.08	1	3.1	0.32	251	[−67, 7584]	0.29
Leukemia[e] (all yrs)	96	92	1.04	146	146	1.00	0	[−23, 30]	0.98
0–5 yrs[f]	67	62	1.09	95	95	1.00	5	[−24, 44]	0.78
≥ 5 yrs[f]	29	31	0.94	51	50	1.01	−8	[−43, 45]	0.73

O: observed; E: expected; RT: radiotherapy; 95% CI: 95% confidence interval.

[a] Second malignancies individually analyzed were buccal, lip, tongue, salivary, gum and other oral sites, oropharynx, nasopharynx, hypopharynx, esophagus, stomach, small intestine, colon, rectum, liver or gallbladder, pancreas, nasal cavities, larynx, lung, breast, testis, kidney, bladder, melanoma, eye, brain or central nervous system, thyroid, endocrine, bone, connective tissue, non-Hodgkin lymphoma, Hodgkin disease, multiple myeloma, acute lymphocytic leukemia, chronic lymphocytic leukemia, acute nonlymphocytic leukemia, acute myelogenous leukemia, and chronic myelogenous leukemia. For brevity, data shown only for those sites for which there was either a significantly increased relative risk for radiotherapy versus surgery (in either direction), or for which there was a nonsignificant increased relative risk of 20% for any time period.

[b] Percent increase in relative risk for radiotherapy (RT) versus surgery $(100\ |1-RR_{RT}/RR_{surgery}|)$, in which the relative risks (RR) are calculated using Poisson models adjusted for age at prostate carcinoma diagnosis and time since prostate carcinoma diagnosis.

Bladder

rectum

Sarcomas

$$RR = \frac{Inc_{RT}}{Inc_{norm}}$$

$$\%\ \text{Incr.Risk} = \frac{Inc_{RT} - Inc_{surg}}{Inc_{surg}} \times 100$$

Brenner, Cancer Jan 2000 , (51584 pz RT; 70539 Surg)

Prostate data from literature

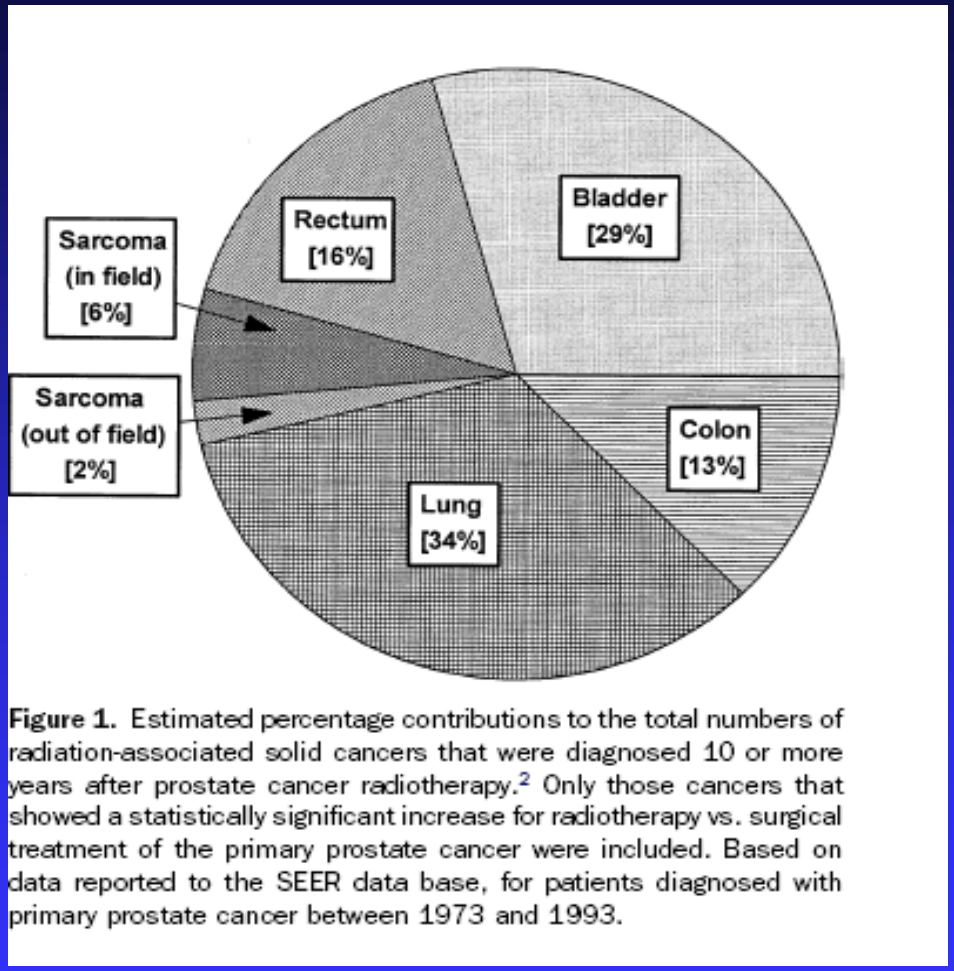


Figure 1. Estimated percentage contributions to the total numbers of radiation-associated solid cancers that were diagnosed 10 or more years after prostate cancer radiotherapy.[2] Only those cancers that showed a statistically significant increase for radiotherapy vs. surgical treatment of the primary prostate cancer were included. Based on data reported to the SEER data base, for patients diagnosed with primary prostate cancer between 1973 and 1993.

Brenner,..;J. Gastro 2005

From these data it comes out that :

Lung dose is two order of magnitude less than rectum and bladder doses, but the RR increase is of the same order

Therefore it would be reasonable that the risk is not a linear, but a plateau, function of the dose, and different organs may demonstrate wide variations in rad sensitivity.

The risk for sarcomas doesn't change greatly for in field and out field volumes (???)

Conclusions :

TABLE 3
Estimated Absolute Numbers of Second Solid Tumors in the Radiotherapy Group Associated with Radiotherapy Treatment

	Persons at risk	Person-years at risk	Estimated no. of solid tumors associated with RT	Estimated RT-associated solid tumors/person at risk	Estimated RT-associated solid tumors/person-years at risk
All years	51,584	218,341	179	1 per 290	1 per 1220 PY
≥ 5 years after diagnosis	17,327	64,700	139	1 per 125	1 per 465 PY
≥ 10 years after diagnosis	5046	15,053	71	1 per 70	1 per 212 PY

RT: radiotherapy; PY: person-years.

Brenner estimate an 0,8% increase, for all solid tumors, of patients surviving between 5 and 10 years and 1,5% for longer lived patients

Cervical Cancer

Local dose administrated by Brachy up to 150 Gy

OAR's doses :

0,1 Gy Thyroid

0,3 Gy Breast

2 Gy Stomach

7 Gy to active Bone marrow

Kleinerman, R.A and others ; Second primary cancer after treatment for cervical cancer (1995) Cancer.

Cervical Cancer

Statistically verified occurrence

cancer site	ERR Gy-1	EAR person/(y *Gy)
Stomach	0,54	3,16E-04
Tyroid	n.s	n.s.
Chronic Lymphocytic Leukemia	n.s	n.s.
Other Leukemias	0,88	?
Rectum and bladder	?	?

Boice and others; 1987; 1988

Data from literature : Breast

Table 1. Cumulative risks of second malignancies at 10 years of follow-up

Localization	Group	Rate (std)	RR (95% CI)	p^*
Sarcoma	RT	0.0026 (0.0005)	7.46 ([1.02–54.52])	0.020
	No RT	0.0000 (0.0000)		
Lung	RT	0.0042 (0.0007)	3.09 ([1.12–8.53])	0.022
	No RT	0.0018 (0.0009)		
Ovarian	RT	0.0056 (0.0008)	1.90 ([0.91–3.94])	0.079
	No RT	0.0026 (0.0011)		
Gynecological	RT	0.0089 (0.0010)	1.30 ([0.81–2.09])	0.284
	No RT	0.0071 (0.0019)		
Genitourinary	RT	0.0021 (0.0005)	0.94 ([0.43–2.03])	0.870
	No RT	0.0025 (0.0010)		
Gastrointestinal	RT	0.0106 (0.0011)	0.76 ([0.54–1.07])	0.118
	No RT	0.0153 (0.0027)		
Head and neck	RT	0.0012 (0.0003)	3.91 ([0.52–29.29])	0.151
	No RT	0.0003 (0.0003)		
Thyroid	RT	0.0014 (0.0004)	1.33 ([0.39–4.53])	0.650
	No RT	0.0016 (0.0009)		
Lymphomas	RT	0.0026 (0.0005)	1.12 ([0.50–2.53])	0.784
	No RT	0.0013 (0.0007)		

Abbreviations: CI = confidence interval; RR = relative risk; RT = radiotherapy.
* Log-rank test; RR and CI: univariated Cox analysis.

The author demonstrates an increase for 2° tumors induction in the lung (+3,09 RR) and sarcomas (+7,46 RR)

Kirova..; IJROBP 2007

Data from literature : Breast

Warning: Also in this case RR is not AR

The figures in the Kirova's paper, derived from a 10,5 years follow up, are :

- 27 sarcomas over 13472 pts RT , with 0 observed cases in the non RT group . That means a percentage of incidence of 0,2%.
- 54 ca lung c. (0,4%) with 4 cases in the not RT group (3233 pts). But among these 58 pts, " 52 having smoke histories (??)".
- Not evidence of an increase of 2° tumors induction in the controlateral breast….

Data from literature : Breast

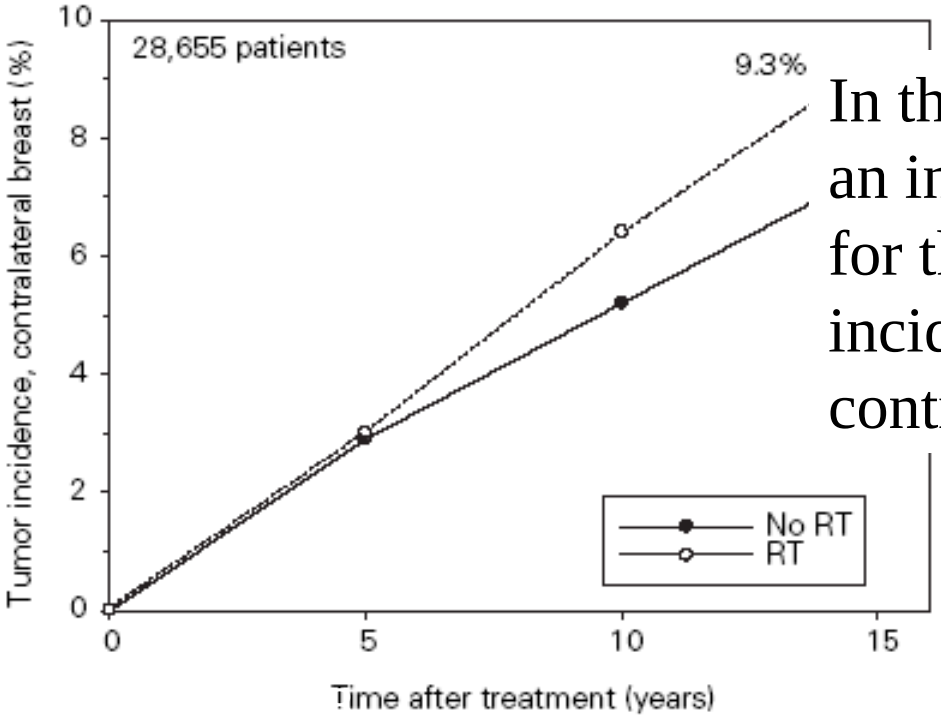


Figure 1. Incidence of contralateral breast cancer. The figure displays the time-to-event for the incidence of tumors in the contralateral breast in patients with breast cancer treated either with surgery alone or with additional irradiation (data from [5], webfigure 7; http://www.ctsu.ox.ac.uk/projects/ebctcg, August 22, 2007).

In this paper the author find an increase larger than 20% for the RR of 2nd tumor incidence in the controlateral breast.

Wolfgang Dorr et al; Second Tumors after oncologic treatments Strahlentherapie und Onkologie; 184(2008) , 67 -72

Data from literature : Breast

is an important public health issue. A recent descriptive analysis of Surveillance Epidemiology and End Results Program (SEER) cancer registries found that breast cancer survivors have an 18% higher risk of developing a subsequent cancer compared with the general population (Curtis *et al*, 2006). Shared environmental and

Le donne che sopravvivono al tumore della mammella hanno un 18% di aumento del rischio di sviluppare un altro tumore rispetto alla popolazione generica

Curtis et al , 2006

Data from literature : Breast (182.000 pts follow up)

Table 2 Risk of second solid primary cancer after invasive locoregional breast cancer in 5-year survivors (SEER 9 registries 1973–2005)

		Surgery + radiotherapy			Surgery only				
Dose grouping[a]	Cancer site	Observed cases	Expected cases	SIR	Observed cases	Expected cases	SIR	RR[b]	(95% CI)
High (1 + Gy)	Oesophagus	56	24.98	2.24*	68	61.58	1.10		
	Pleura	2	0.22	9.14*	0	0.50	0		
	Lung	814	673.16	1.21*	1,387	1582.33	0.88*		
	Bone	13	4.14	3.14*	17	9.33	1.82*		
	Soft tissue[c]	56	18.95	2.96*	48	42.50	1.13		
	Sub-total	941	721.50	1.30*	1520	1697.63	0.90*	1.45	(1.33–1.58)
Medium (0.5–0.99 Gy)	Stomach	56	54.18	1.02	158	138.36	1.14		
	Liver/gall bladder	35	61.90	0.57*	110	147.33	0.75*		
	Larynx	10	19.35	0.52*	35	47.27	0.74		
	Thyroid	72	62.78	1.15	129	122.43	1.05		
	CNS	4	2.76	1.45	8	6.13	1.31		
	Sub-total	177	200.98	0.88	440	461.75	0.95	0.89	(0.74–1.06)
Low (<0.5 Gy)	Oral cavity	61	64.74	0.94	147	158.72	0.93		
	Salivary gland	16	8.85	1.81*	24	20.26	1.18		
	Colon	364	387.89	0.94	921	975.15	0.94		
	Rectum	118	128.31	0.92	285	320.40	0.89		
	Pancreas	103	115.47	0.89	268	281.74	0.95		
	Melanoma of the skin	125	118.12	1.06	249	248.37	1.00		
	Cervix uteri	30	52.46	0.57*	75	124.08	0.60*		
	Ovary	219	152.42	1.43*	462	362.68	1.27*		
	Endometrial	421	301.52	1.40*	878	705.96	1.24*		
	Other female genital	33	37.45	0.88	80	88.47	0.90		
	Bladder	125	113.19	1.10	287	273.89	1.05		
	Kidney	71	85.30	0.83	170	191.37	0.89		
	Renal/other urinary tract	9	14.51	0.62	33	36.66	0.90		
	Brain	45	44.92	1.00	78	107.10	0.73*		
	Other sites	71	74.34	0.96	161	168.79	0.95		
	Sub-total	1811	1699.50	1.07*	4118	4063.64	1.01	1.01	(0.95–1.07)
All solid cancers (excluding contralateral breast)		2929	2621.98	1.12*	6078	6223.02	0.98	1.11	(1.06–1.16)
Contralateral breast		2076	688.07	3.02*	4415	1571.94	2.81*	1.09	(1.04–1.15)

Abbreviations: CI = confidence interval; CNS = central nervous system; SIR = standardised incidence ratio = ratio of observed to expected cases. [a]Mean doses on the basis of tangential fields breast radiotherapy, see Table 1. *$P < 0.05$. [b]RR = relative risk calculated using Poisson regression stratified by stage, age at treatment, year of treatment, chemotherapy and hormonal therapy. [c]Soft tissue histology: surgery + radiotherapy includes 16 angiosarcomas, 22 fibrosarcomas, 18 others and surgery only includes 2 angiosarcomas, 18 fibrosarcomas and 28 others.

Berrington et al; Second solid cancers after radiotherapy of breast cancer in SEER Cancer registries; British Journal of Cancer (2010), 102, 220 – 226.

Data from literature : Breast

Table 3 Risk of subsequent primary solid cancer at highly exposed sites (>1 Gy: oesophagus, pleura, lung, bone, connective tissue) after invasive locoregional breast cancer in 5-year survivors (SEER 9 registries: 1973–2005)

	Surgery + radiotherapy			Surgery only					
Characteristic	**Observed**	**Expected**	**SIR**	**Observed**	**Expected**	**SIR**	**RR[a]**	**(95% CI)**	**P-trend/ homogeneity**
Age at diagnosis									
<40	45	17.33	2.60	50	47.07	1.06	2.67	(1.75–4.07)	
40–49	195	119.86	1.63	310	318.74	0.97	1.67	(1.38–2.02)	
50–59	310	251.87	1.23	542	625.41	0.87	1.40	(1.21–1.62)	
60+	391	332.45	1.18	618	706.41	0.87	1.31	(1.15–1.50)	<0.001
Year of diagnosis									
1973–1982	268	168.17	1.59	646	735.03	0.88	1.77	(1.52–2.05)	
1983–1992	415	336.02	1.24	672	763.30	0.88	1.40	(1.24–1.59)	
1993+	258	217.30	1.19	202	199.30	1.01	1.15	(0.95–1.38)	0.01
Latency									
5–9 years	488	406.05	1.20	685	750.51	0.91	1.30	(1.15–1.47)	
10–14 years	268	190.88	1.40	455	485.07	0.94	1.51	(1.30–1.77)	
15+ years	185	124.57	1.49	380	462.05	0.82	1.80	(1.50–2.16)	<0.001
Disease stage									
Localised	594	484.66	1.23	1051	1187.53	0.89	1.40	(1.25–1.55)	
Regional	347	236.85	1.47	469	510.01	0.92	1.55	(1.35–1.80)	0.24
Surgery (1980+)[b]									
Breast conserving	550	467.39	1.18	874	962.6	0.91	1.28	(1.14–1.43)	
Mastectomy	123	85.94	1.43				1.50	(1.22–1.82)	>0.5[c]

Abbreviations: CI = confidence interval; SIR = standardised incidence ratio = ratio of observed to expected cancers. [a]RR = relative risk calculated using Poisson regression with stratification by stage, age at treatment, year of treatment, chemotherapy and hormonal therapy. [b]Comparison group of surgery only was on the basis of breast conserving surgery and mastectomy combined. [c]Estimated using methods that account for shared comparison group (Berrington and Cox, 2003).

Data from literature : Breast

Table 4 Risk of contralateral breast cancer after invasive locoregional breast cancer in 5-year survivors (SEER 9 1973–2005)

	Surgery + radiotherapy			Surgery only					
Characteristic	**Observed**	**Expected**	**SIR**	**Observed**	**Expected**	**SIR**	**RR[a]**	**(95% CI)**	**P-trend/ homogeneity**
Age at diagnosis									
<40	277	41.05	6.75	490	97.15	5.04	1.30	(1.11–1.50)	
40–49	517	166.07	3.11	1089	377.01	2.89	1.08	(0.97–1.20)	
50–59	598	233.21	2.56	1437	542.25	2.65	0.98	(0.89–1.08)	
60+	684	247.74	2.76	1399	555.53	2.52	1.14	(1.04–1.26)	0.03
Year of diagnosis									
1975–1982	557	160.34	3.47	2083	685.68	3.04	1.12	(1.02–1.23)	
1983–1992	964	318.28	3.03	1849	699.15	2.64	1.14	(1.05–1.23)	
1993+	555	209.46	2.65	483	187.11	2.58	1.04	(0.92–1.18)	0.02
Latency									
5–9 years	1233	401.61	3.07	2194	736.14	2.98	1.06	(0.99–1.14)	
10–14 years	554	179.78	3.08	1236	450.07	2.75	1.12	(1.01–1.24)	
15+ years	289	106.68	2.71	985	385.73	2.55	1.04	(0.91–1.19)	0.1
Disease stage									
Localised	1337	454.98	2.94	2988	1088.40	2.75	1.10	(1.03–1.18)	
Regional	739	233.09	3.17	1427	483.54	2.95	1.08	(0.98–1.18)	>0.5
Surgery type (1980+)[b]									
Breast conserving	1256	442.25	2.84	2332	886.26	2.63	1.10	(1.03–1.18)	
Mastectomy	263	85.49	3.08				1.11	(0.97–1.26)	>0.5[c]

Abbreviations: CI = confidence interval; SIR = standardised incidence ratio = ratio of observed to expected cancers. [a]RR = relative risk calculated for treatment with surgery + radiotherapy compared with surgery alone using Poisson regression with stratification by stage, age at treatment, year of treatment, chemotherapy and hormonal therapy. Women with bilateral breast cancer at diagnosis or unknown laterality were excluded. [b]Comparison group of surgery only was on the basis of breast conserving surgery and mastectomy combined. [c]Calculated using methods to account for the shared comparison group (Berrington and Cox, 2003).

Berrington et al; Second solid cancers after radiotherapy of breast cancer in SEER Cancer registries; British Journal of Cancer (2010), 102, 220 – 226.

Data from literature : Breast

Table 5 Estimated number of excess solid cancers, attributable risk and excess absolute risk (EAR) per 10 000 person-years related to radiotherapy in those treated with surgery + radiotherapy for invasive locoregional breast cancer[a] (SEER 9 registries: 1973–2005)

		Excess cancers		Attributable risk		EAR/10 000 P-Y	
	Total second cancers	*n*	(95% CI)	%	(95% CI)	*n*	(95% CI)
Contralateral breast cancer							
5 + -year survivors (RT + surgery)	2076	176	(69–284)	8	(3–14%)	5	(2–7)
1 + -year survivors (RT + surgery)	3775	176	(69–284)	5	(2–8%)	2	(1–4)
All other solid cancers							
5 + -year survivors (RT + surgery)	2929	292	(222–362)	10	(5–14%)	8	(6–9)
1 + -year survivors (RT + surgery)	5089	292	(222–362)	6	(4–7%)	4	(3–5)

Abbreviations: CI, confidence interval; P–Y = person-years; RT = radiotherapy. [a]Analyses assume a 5 + -year minimum latent period for radiation-related solid cancers and, therefore, no excess cancers related to radiation would occur in the 1–5-year interval. Therefore, only the denominator (total second cancers) changes in the two analyses.

Berrington et al; Second solid cancers after radiotherapy of breast cancer in SEER Cancer registries; British Journal of Cancer (2010), 102, 220 – 226.

Data from literature : Breast (data from 42,000 women follow up)

dence of SPM 20% higher in irradiated women than in women not submitted to radiation therapy (SIR = 1.20). There was a significant excess for lung (SIR = 1.61), esophagus (SIR = 2.06), soft tissue sarcoma (SIR = 2.34) and leukemia (SIR = 1.71) but no excess for melanoma, bone sarcoma, colorectal, stomach, kidney, uterus and thyroid cancers.

$$SIR = \frac{N_{\text{observed}}}{N_{\text{expected}}(age, gender, tissue, SIRpop)}$$

SIR =: Standardaized Incidence Ratio

Clarke M.; Effects of radiotherapy ..for early breast cancer…; Lancet 2005; 366: 2087-106

Hodgkin's disease and Lymphoma

As compared to general population the RR of second cancer , in pts treated by RT for HDL and not HDL, is more than doubled

The RR for breast cancer is the highest in particular among young women: Range 6 – 60, decreasing the age from 30 to 16 years.

HD Lymphomas

Lung cancer [1 OR 5,9 (NO CHT) (rapporto tra gli odds dei non ammalati rispetto agli ammalati) per dosi < 5Gy

Breast Cancer[2 OR 3,2 per dosi superiori ai 4 Gy

1 Travis and coll ; Lung cancer following CHT and RT for Hodgkins's disease. J. Nat. Cancer 94(2002); 182 – 192

2 Travis and coll ; Breast Cancer following CHT and RT among young women with Hodgkins's disease. J. Am. Med Association (2003)); 465-475

Thyroid cancer

An excess of second cancers was observed following the treatment either by external Beam or by radioiodine.(1

SIR 1,45 (ghiandole salivari, genitali, reni e surreni) (2

Leukemia (dmed al bone marrow 0,34 Sv) and colon cancer incidences were increased in pts. treated by radio iodine(1 .

Altri autori non hanno rilevato invece alcun aumento dell'incidenza di leucemie per pz trattati con I131 per K tiroideo(3

1. M. Tubiana; Can we reduce the incidence of SPM after RT; R&O 2009, doi 10.1016.
2 Hall and others ,Cancer risks in thyroid cancer patients. 1991 Brit. J Cancer 64: 159 -163
3 Vathaire and others ; Leukemias and cancers following iodine administration for thyroid cancers; Brit. J. of cancer 1997

Soft Tissue Sarcoma (induction)

Sarcomas are induced by High doses (> 48 Gy)

The dose effect relationship is curvilinear. Probably quadratic. The delay is quite long up to 35 years.

M. Tubiana; Can we reduce the incidence of SPM after RT; R&O 2009, doi 10.1016.

Pediatrics

Table 1. Characteristics of the 4,401 patients treated for a childhood cancer

General information	
Number of patients recruited in France/Great Britain	3189 / 1212
Mean year of treatment (min–max)	1974 (1942–1985)
Number of men / women	2432 / 1969
Mean age at diagnosis of first cancer, years (min–max)	6.1 (0–16)
First cancer treatment: number of patients (%)	
Radiotherapy alone	1045 (23.7)
Chemotherapy alone	885 (20.1)
Surgery alone	406
Radiotherapy + chemotherapy	2065 (46.9)
Follow-up	
Mean duration in years (min–max)	15 (3–48)
Number of patients lost to follow-up in 1992 (%)	532 (12)
10-year overall survival, % (95% CI)	90.8 (90.4–91.3)
20-year overall survival, % (95% CI)	85.4 (84.8–86.1)
Number of relapses (%)	589 (13.4)
Second cancer	
Number of patients	124
Time between first cancer and second cancer, years (min–max)	11 (3-37)
25-Year cumulative incidence, % (95% CI)	5 (4.4–5.6)

F Nguyen,Risk of a second malignant Neoplasm after cancer in childhood ….., IJROBP 2008

Organ dose and tumor induction

primay cancer irradiated organ	2nd tumor site	ERR Gy^{-1}
cervical	stomach	1,08
breast	stomach	1,3
tymus	breast	2,48
Hodgkin	breast	0,15
Hodgkin	lung	0,15
breast	lung	0,2

ERR = RR- 1

ERR = 1 Means a doubling of the tumor in the exposed population.

When considering a mean dose to 2nd organ of 10^{-3} the target dose it means a risk of the order of 1,08 *50*10^{-3} =5%

X George Xu, A review of dosimetry studies on external beam radiation treatment with respect to second cancer induction; PMB, 53(2008)

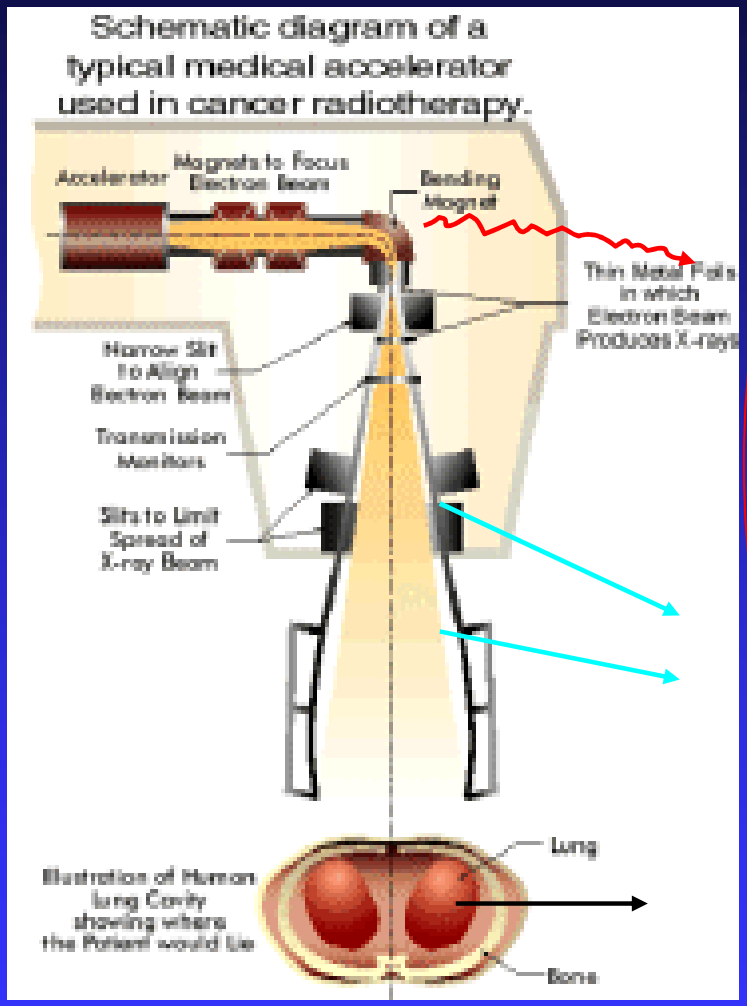
Absolute and RR site by site

Site of primary cancer	Treatment modality	Risk qualitatively	estimated risk
Hodgkin Limphoma	3DCRT	very high	2,0 RR (Doubled)
Breast	3DCRT	high	1,11 RR all solid canc 1,19 RR controlateral
Pediatrics	3DCRT	medium - high	5 - 25 % AR
Prostate	IMRT	medium	5 % AR
Prostate	3DRCT	low	2 % AR
Tyroid	Radio Iodine - 3DCR	low	1,45 RR
Head & Neck	3DRCT - IMRT	low	1 - 1,5 % AR

La fisica dei fasci e delle radiazioni :

La loro influenza

Peripheral dose



Leakage

Head Scatter

Patient Scatter

Function of : geometry, energy, MUs and collimation geometry.

These components dominate far from PTV

Function of field area and beam energy: dominates in the closeness of PTV.

Technique comparison

Table 1. Lifetime probabilities of developing fatal secondary malignancies by organ site*

Organ	Probability of fatal cancer (%/Sv)
Bladder	0.30
Bone marrow	0.50
Bone surface	0.05
Breast	0.20
Esophagus	
Colon	
Liver	
Lung	
Ovary	
Skin	
Stomach	
Thyroid	
Remainder of t	
Total	

* From NCRP Report 116 (13) for entire population.

We recently determined (with measurements in a Rando phantom and with gold foils [4]) the photon and neutron dose equivalents to 7 organs resulting from a variety of treatment techniques for prostate cancer. A total of 11 anatomic sites were examined in the colon, liver, stomach, esophagus, lung, thyroid, and active bone marrow. Seven treatment strategies were investigated: 1

Kry et al IJROBP 2005

Technique comparison

IMRT brings to a doubling of the lifetime Risk

Table 5. Maximal total dose equivalents for each treatment (all fractions, in mSV) and corresponding lifetime risk of fatal secondary malignancy (in %)

	Treatment type, energy, and accelerator						
	Conventional	Intensity-modulated radiotherapy					
	18 MV	6 MV		10 MV	15 MV		18 MV
Organ site		Varian	Siemens	Varian	Varian	Siemens	Varian
Colon	527	965	1148	655	877	1103	1271
Liver edge	462	930	1148	661	974	1135	1391
Stomach edge	431	699	893	458	810	920	1154
Liver center	265	417	552	344	541	643	869
Stomach center	253	419	533	334	549	610	860
Esophagus edge	252	437	552	333	509	587	770
Lung edge	228	311	484	287	492	610	910
Lung center	138	189	366	189	314	466	560
Esophagus center	105	161	347	166	232	350	439
Thyroid	139	130	372	134	313	448	684
Bone marrow	359	466	639	363	765	812	1213
Percent risk of fatal second malignancy	1.7	2.9	3.7	2.1	3.4	4.0	5.1

3DCRT

IMRT

Kry et al IJROBP 2005

2nd cancer induction

Table 3 — Risk of fatal radiation-induced malignancy after radiotherapy for prostate cancer (%/Sv)

Hall and Wu [4]	
Conventional 6 MV	1.5
IMRT 6 MV	3.0
Kry *et al.* [5]	
Conventional 18 MV Varian	1.7
IMRT 6 MV Varian	2.9
Siemens	3.7
IMRT 10 MV Varian	2.1
IMRT 15 MV Varian	3.4
Siemens	4.0
IMRT 18 MV Varian	5.1

IMRT, intensity-modulated radiotherapy.

Hall E. Clinical Onc. 2006

IMRT may increase the incidence of solid cancers in long-term survivors from ≈ 1-2% to ≈ 2-5% ⇒ extimations based on LINEAR relationship 5% Sv^{-1}(?? Overestimated ??)

From these data IMRT would bring to a risk increase, determined by :

- Greater number of fields: that is a greater irradiated volume when compared to 3DCRT
- Leakage radiation increase as consequence of the MU increase

The techniques with X rays energies > 15MeV are definitively cancelled from IMRT

…But pay attention

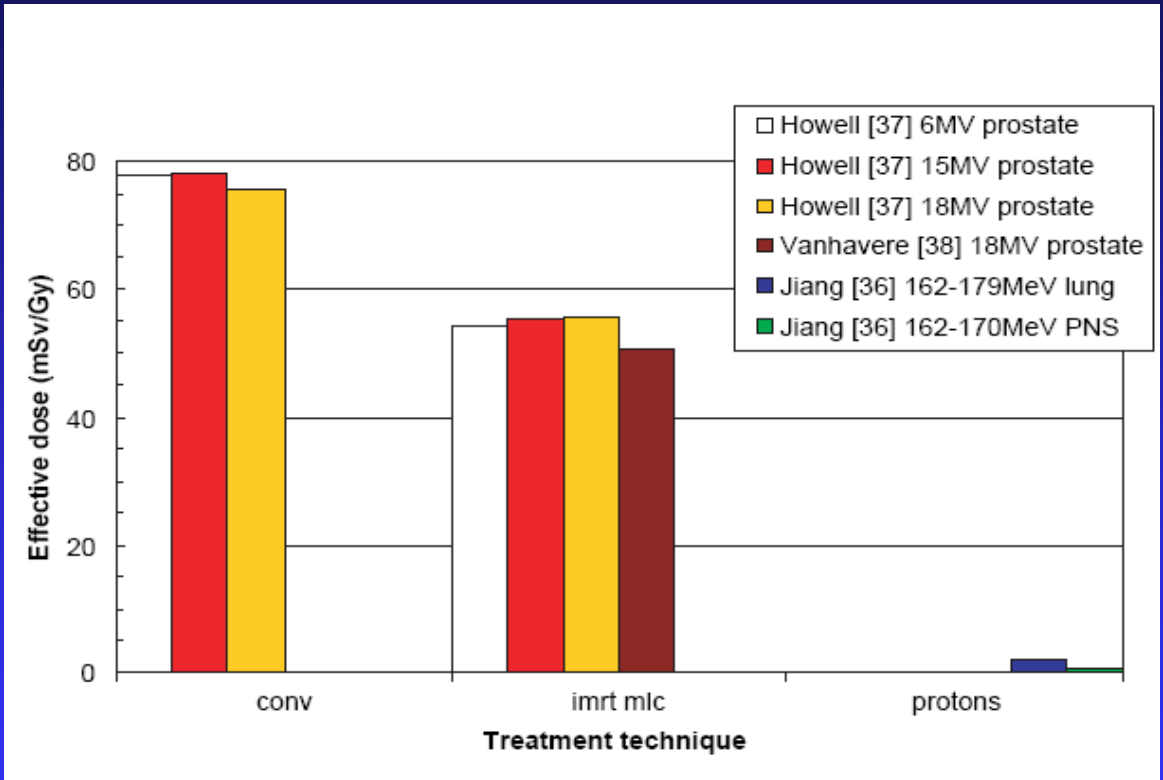
Even if the risk of 2° tumors induction is still a low risk, it is remarkable the possibility to verify if, when a comparable dose distribution is obtainable between 3DCRT and IMRT, it would not be better the traditional methodology. As for example in the treatment of breast, lung and upper abdomen region

Moreover all theese data have to be considered with a considerably uncertanty margin

Rubens , infact , demonstrates that is not self evident a risk increase in the treatment of the Neck tumors. In several cases, when a similar number of fields with smaller area is used, it is possible to obtain a decrease in the scattered component to balance the increase of the leakage

Ruben, IJROBP 2008

Comparison 3DCRT - IMRT and Protons



Palm; Acta Oncologica 2007

In-field radiation: Integral dose

- Data from treatment planning studies
- Direct radiation: planning data on patient volume included in the CT scan
- Integral dose: non-target tissue average dose times volume (CT scan)

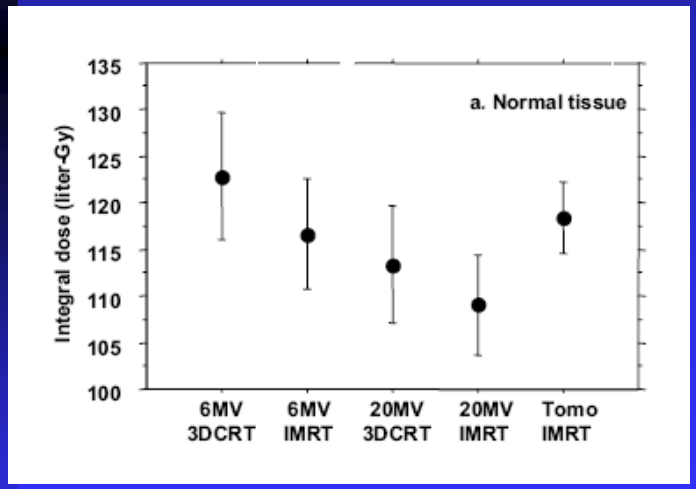
Author	Disease,	Technique	Integral dose (GyxLiter)
Mock 2004	Nasoph, 5 Pts	CRT	17% of Dpres
		IMRT	15% of Dpres
		3D-PROTONS	9% of Dpres
Cozzi 2007	Intracranial, 12 PTs	STEREO-RT, 6MV	9.3±2.5
		IMRT, 6 MV	12.2±3.4
		AMOA, 6 MV	7.3±2.8
		CYBER, 6 MV	4.1±3.1
		HT, 6 MV	5.4±1.9
Fiorino 2007	Nasoph., 6 PTs	IMRT, 6 MV	126
		HT	134
Fiorino 2006	H&N, 5 PTs	IMRT, 6 MV	112.6±15.7
		HT	119.7± 14.9
Widesott sub. *	Nasoph 6 PTs	HT, 6 MV	21.2±7.0
		IMPT	12.6±4.4

In-field radiation: integral dose (II)

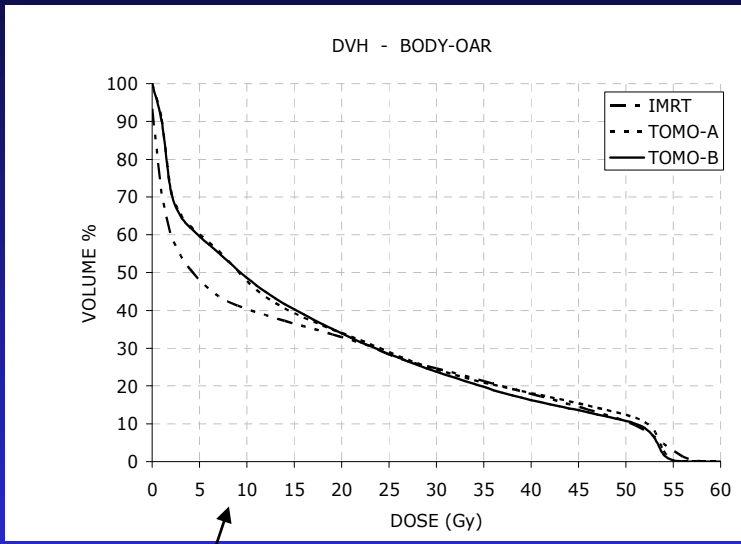
Author	Disease,	Technique	Integral dose (GyxLiter)
Pizkall 2000	Complex cases, 9 PTs	3DCRT	1 Rel data
		IMRT	1.2 Rel data
Lomax 1999	Various, 11Pts	CRT	3 Rel data
		IMRT	2 Rel data
		IMPT	1 Rel data
AoYama 2006	Prostate, 5 PTs	CRT, 6 MV	122.8
		IMRT, 6 MV	116.7
		CRT, 20 MV	113.4
		IMRT, 20 MV	109.1
		HT, 6 MV	117.9
Iori 2008	Prostate, 6 PTs	HT, 6 MV	165±14
		IMAT, 6 MV	125±11

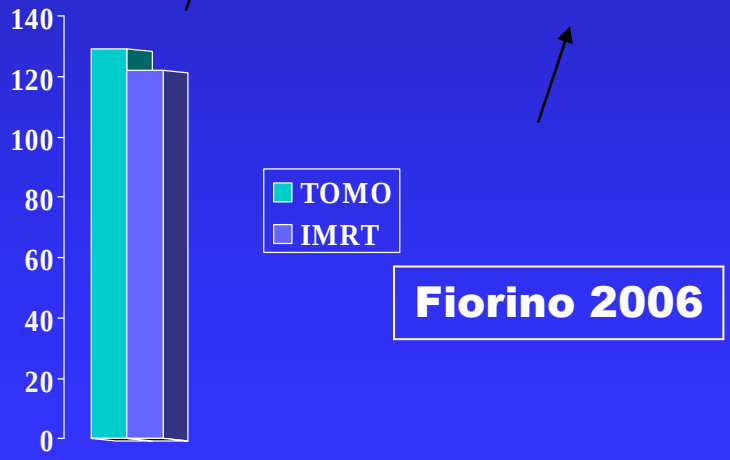
IN Field : IMRT vs Tomotherapy

- In most clinical cases in-field integral dose with Tomo is comparable to IMRT



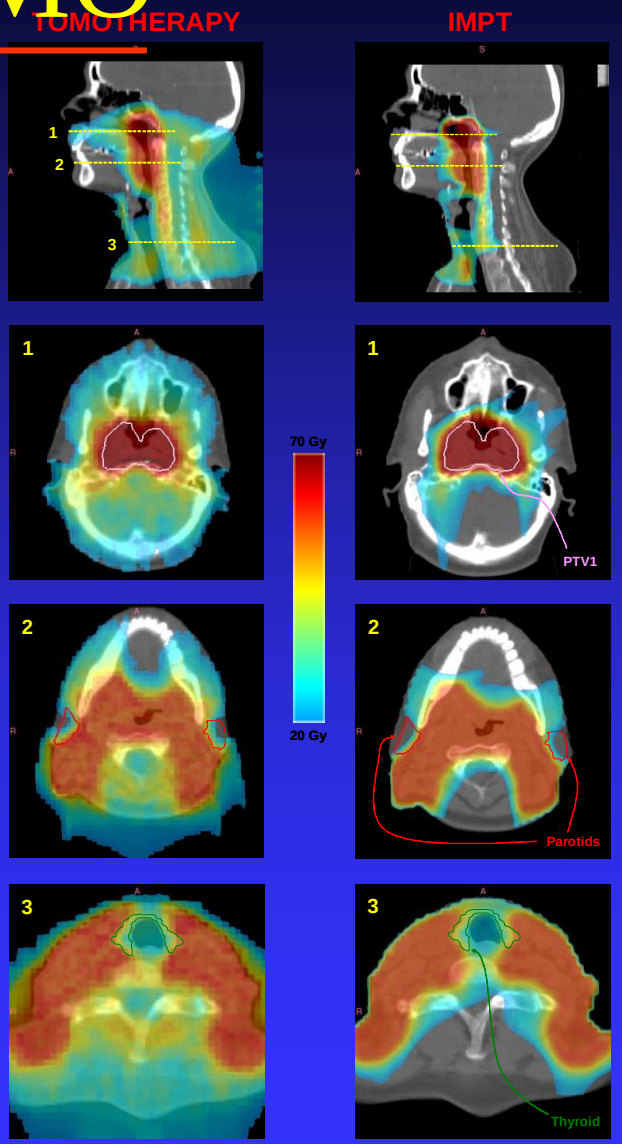
Fiorino C, et.al ***Significant improvement in normal tissue sparing and target coverage for head and neck cancer by means of helical tomotherapy.***
Radiother Oncol ,2006 Mar;78(3):276-82





IN Field : IMPT vs TOMO

- Active IMPT systems may reduce the integral dose of a factor 2-3
- Passive scattering may be affected by significant neutron contamination (Hall 2005) that may reduce the benefits of the reduction of the low-dose bath



Widesott, et al ;Comparing protons and tomotherapy for HN patients IJROBP 72(2008) : 588-596

OUT FIELD

- Out-of-field Dose increases when increasing the number of Monitor Units (Head scatter+leakage)…as in IMRT
- Out-of-field Dose increases with energy

Out Field doses

Negligible variations between IMRT e 3DCRT.

Variations larger than a factor 10 between photons and scanning beam protons

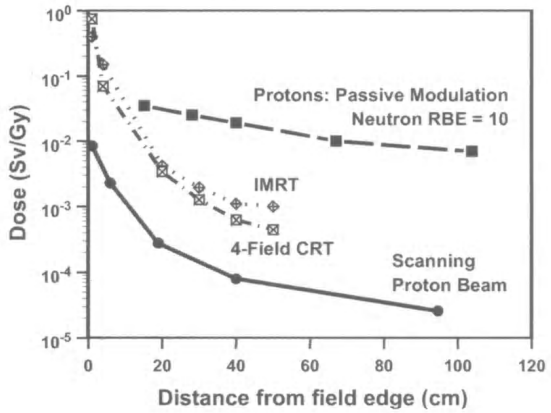


Fig. 10. The equivalent dose outside the edge of the treatment field as a fraction of the dose at the isocenter for protons with passive modulation, for a scanning proton beam, and for 6-MV X-rays, either 4-field conformal radiation therapy (CRT), or intensity-modulated radiation therapy (IMRT). The doses are rough estimates and are likely to be highly facility dependent. The passive-modulation: proton data are from Yan *et al*. (19), renormalized to a 10-cm × 10-cm field and to a neutron relative biologic effectiveness (RBE) or quality factor of 10. The pencil-beam scanning proton data are from Schneider *et al*. (18), renormalized to a 10-cm × 10-cm field and an RBE or quality factor of 10. Both proton

OUT FIELD DOSE in Prostate

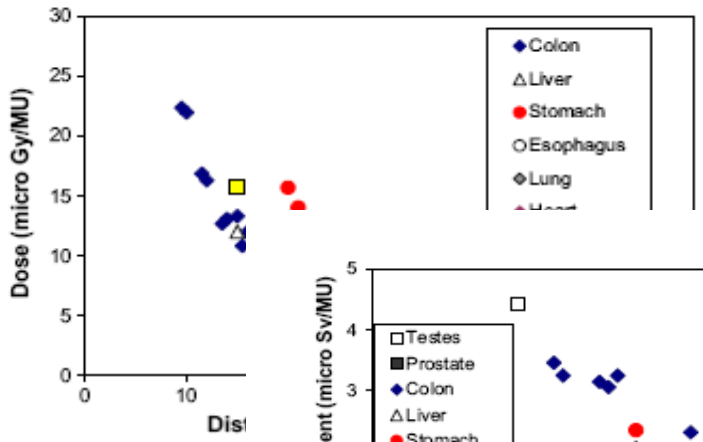
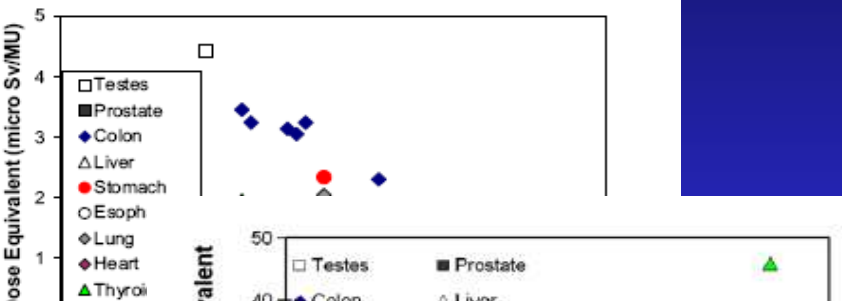


Fig. 3. Out-of-field photon dos
Data include calculated dose
published previously [5].



Conclusions: The risk of secondary malignancy associated with high-energy radiation therapy may not be as large as previously reported, and likely should not deter the use of high-energy beams. However, the large uncertainties in neutron dose equivalents at specific locations within the patient warrant further study so that the risk of secondary cancers can be estimated with greater accuracy.

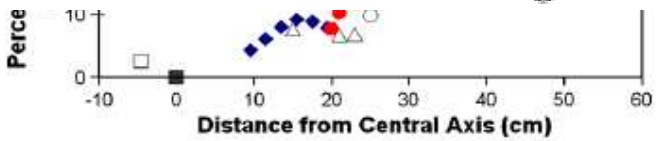


Fig. 5. Percent of the total out-of-field dose equivalent generated by neutrons in the current Monte Carlo model.

Please cite this article in press as: Kry SF et al., Monte Carlo study shows no significant difference in second cancer risk between ..., Radiother Oncol (2009), doi:10.1016/j.radonc.2008.11.020

At last but not least :

Hypo vs. Normo Frazionamento

HYPO IMRT vs standard fractionated 3DCRT

Where is the maximum risk

The critical volumes are in the field edge area: the volumes where doses between 3 – 5 Gy are absorbed In this region, the sublethal radiation effects, would bring the risk for sarcomas induction from 9,0E-05 to 2,1E-02

G. Lawrence, ESTRO 2007 BarcellonaPresentazione orale

HYPO IMRT vs standard fractionated 3DCRT

Data seem to suggest that there is a threshold, in fractionated radiotherapy , for SPM, at 0,6 Gy in adults, and at 0,1 Gy after acute irradiation in children.

Con una “quasi” soglia tra 0,12 e 0,15 Gy/fz.

Quindi l’Hypo può funzionare se :

- Riduce la dose totale
- Riduce (con IMRT e/o 3DCRT il volume sopra 2- 5 %)

Moreover SPM incidence appears to be low for cumulative doses < 3,5 Gy (5% isodose).

M. Tubiana; Can we reduce the incidence of SPM after RT; R&O 2009, doi 10.1016.

RESEARCH Open Access

Hypofractionated radiotherapy has the potential for second cancer reduction

Uwe Schneider[1,2*], Jürgen Besserer[1], Andreas Mack[1]

Schneider *et al. Theoretical Biology and Medical Modelling* 2010, **7**:4
http://www.tbiomed.com/content/7/1/4

HYPO IMRT vs standard fractionated 3DCRT

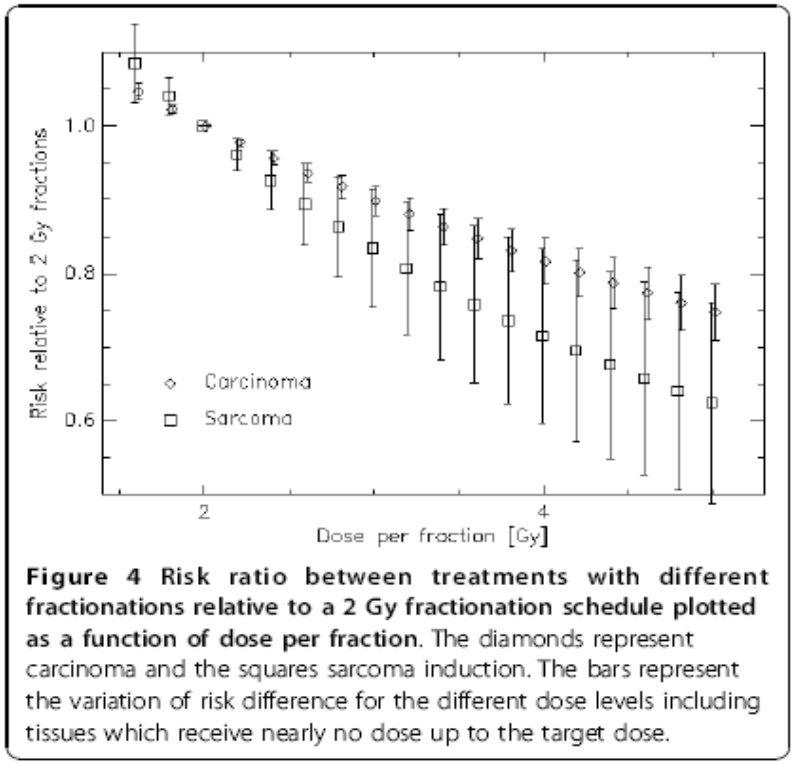


Figure 4 Risk ratio between treatments with different fractionations relative to a 2 Gy fractionation schedule plotted as a function of dose per fraction. The diamonds represent carcinoma and the squares sarcoma induction. The bars represent the variation of risk difference for the different dose levels including tissues which receive nearly no dose up to the target dose.

HYPO IMRT vs standard fractionated 3DCRT

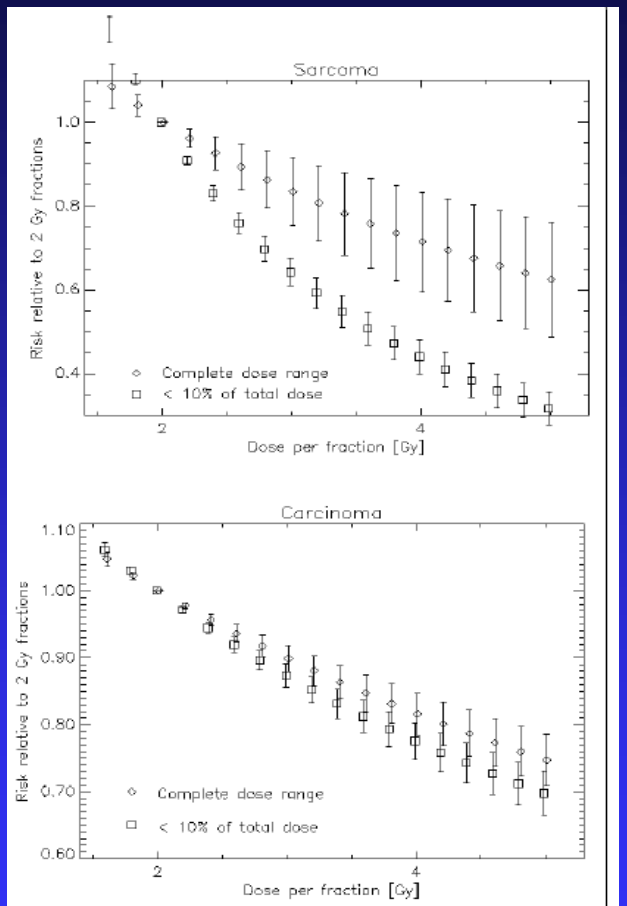


Figure 5 Risk ratio between a treatments with different fractionations relative to a 2 Gy fractionation schedule and plotted as a function of dose per fraction. For sarcoma in a) and for carcinoma in b). The diamonds represent the average over the whole dose range and the squares are averages up to 10% of the target dose which is 5 Gy NTD2 in this example. The bars represent the variation of risk ratio over the dose range.

Conclusions

Induced cancers increase with time after radiotherapy… up to1,5% at 10 years after treatment. This figure may be doubled by new techniques, such as IMRT. In pts in the 60s or 70s doubling the second cancer incidence from 1,5% to 3% may be acceptable if it is balanced by an improvement in the local control and reduced toxicity. Although these improvements have not yet been documented in controlled clinical trials, there seems every prospect that they will materialize in due course.

Be carefull Hall assumes that between 0,1 and 3 Gy the risk increases linearly (LNT)…. This is not demonstrated therefore his conclusion could overestimates the risk from IMRT.

Conclusions

- Childhood RT, also for conventional RT, demonstrates a risk so high that a doubling is not acceptable

- For these treatments we would modify the treatment units as follows :

  - ✓Increasing the head shielding
  - ✓Adding moveable primary collimators to follow the MLC dynamic
  - ✓Cancelling the flattening filter

In order to obtain reduction of scattered and leakage radiation

Alternatively the solution for these treatments is IMPT

Conclusions

The philosophical evolution of Radiotherapy is well represented by the sentence :

The aim of the treatment should be to deliver the minimal effective radiation therapy rather than the maximal tolerable dose.

Grazie per la vostra attenzione